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The clinical implication of cell migration in liver transplantation

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Whole organ transplantation practices have brought this form of surgical treatment to a high level of efficiency and success, contrary to the pessimistic predictions at the outset of most immunologists. Historically, an allograft was envisioned as defenseless and vulnerable to immunologic attack in proportion to its histocompatibility disparity with that of the recipient. This dogma defined transplantation in terms of a unidirectional immune reaction both for bone marrow and organs (a one-way paradigm) (Figure 1).

The one-way paradigm was unchallenged for more than 3 decades until in 1992, we discovered the presence of ubiquitous low level donor leukocyte chimerism in our human organ recipients as long as 30 years post-transplantation (1,2). We postulated from these findings (and subsequently obtained much confirmatory evidence [3-5]) that the interaction of 2 coexisting donor and recipient leukocyte populations, each to the other, was the generic mechanism of successful tolerance after bone marrow transplantation as well as the "acceptance" of organ allografts (Figure 2).

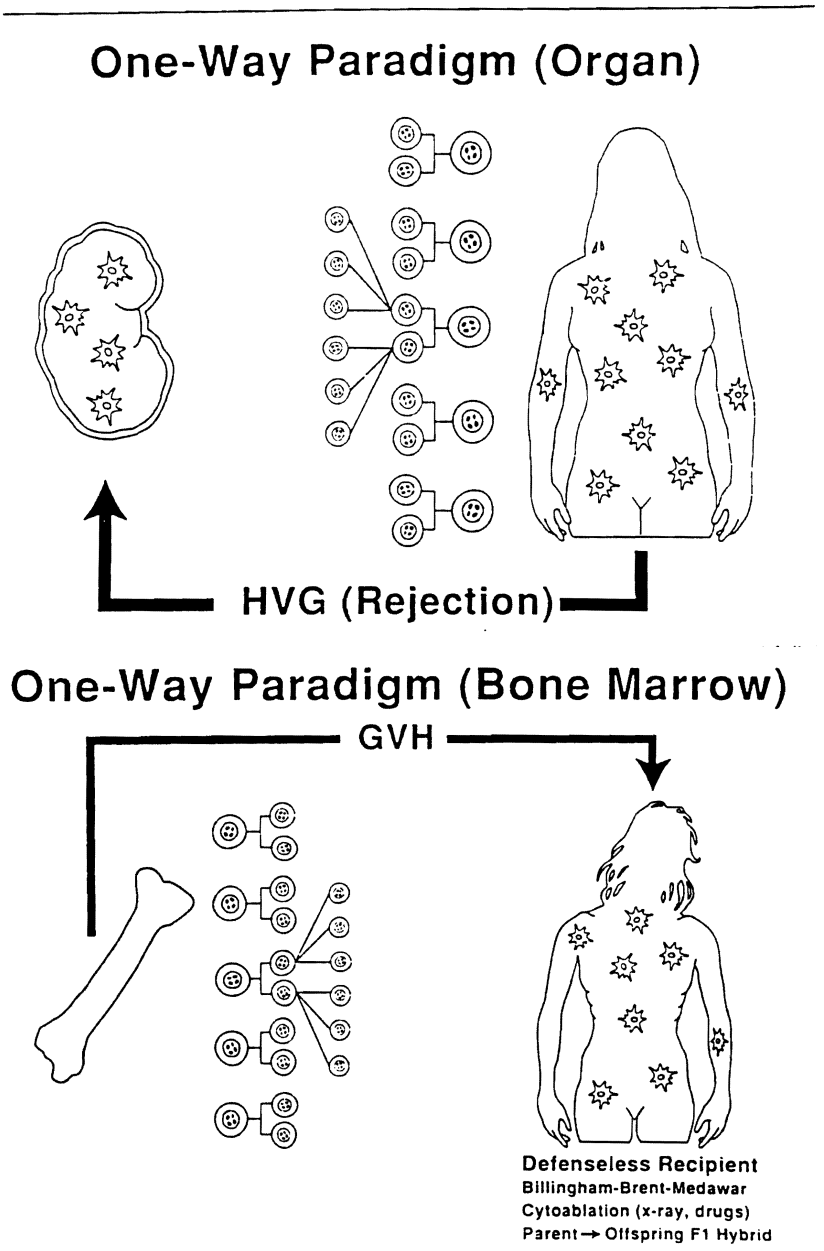

FIGURE 1

The phenomenology of microchimerism has been widely verified in experimental models. The mutual cancelling effect of the coexisting cell populations explains: the blurring of an MHC matching effect on outcome of organ transplantation, the ability to transplant histoincompatible liver, intestine, and bone marrow to the non-cytoablated recipient without causing GVHD, and the ability to stop immunosuppression in many organ recipients (1,2,6). Most importantly, this concept provides a fresh

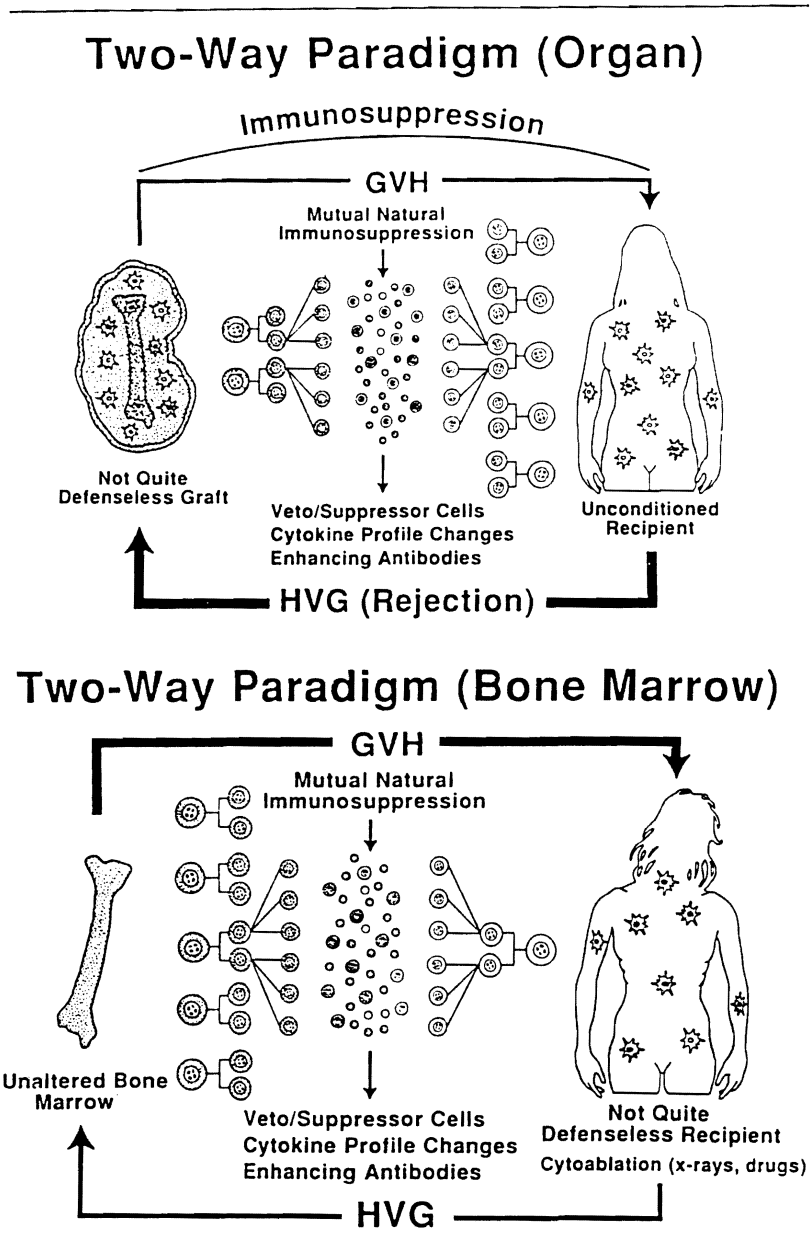

FIGURE 2

context to exploit basic immunologic information in xenotransplantation and other initiatives.

This "2-way (bidirectional) paradigm" has been under intense examination because it has mandated reexamination of transplantation immunology at every level. First, the 2-way paradigm established the long sought linkage between the whole organ transplant practices that were evolved empirically and the neonatal acquired immunologic tolerance

originally described more than 40 years ago by Billingham, Brent, and Medawar (7,8). The discoveries of spontaneous chimerism gave startling insight into what was actually being accomplished with whole organ transplantation, and this will be reviewed in a historic context.

More importantly, these discoveries have illuminated the future (9). The mechanisms leading to chimerism and govern allograft acceptance also ultimately determine the outcome after xenotransplantation. Although it will be difficult to first breech the humoral barrier, manipulating the individual limbs of the two-way reaction (host vs graft and graft vs host) is expected to be the key to the ultimate successful use of animal organs in humans.

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